Novel aspects of the chemistry of tosylmethyl isocyanide

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CHAPTER 6

Novel Syntheses of *N*-(Dimethylsulfamoyl)aldimines and 4(5)-Monosubstituted Imidazoles[1]

Abstract : *4(5)-Monosubstituted imidazoles (**6.10**) have been prepared via base-induced cycloaddition of tosylmethyl isocyanide (TosMIC) to N-(dimethylsulfamoyl)aldimines (**6.4**) or N-tosylaldimines (**6.5**). N-(Dimethylsulfamoyl)aldimines, a new type of shelf-stable aldimines, are readily prepared from aldehydes and N-(dimethylsulfamoyl)amide (**6.8**) in refluxing toluene. N-(Dimethylsulfamoyl)imidazoles (**6.9**) are the initial products from the reaction of TosMIC and aldimines **6.4**. The dimethylsulfamoyl group of the imidazoles **6.9** is readily removed by aqueous HBr to give 4(5)-monosubstituted imidazoles **6.10**. In the case of N-tosylaldimines (**6.5**), the tosyl group of the N-tosylimidazoles (**6.12**) is lost spontaneously to give 4(5)-monosubstituted imidazoles (**6.10**) in one operation.*

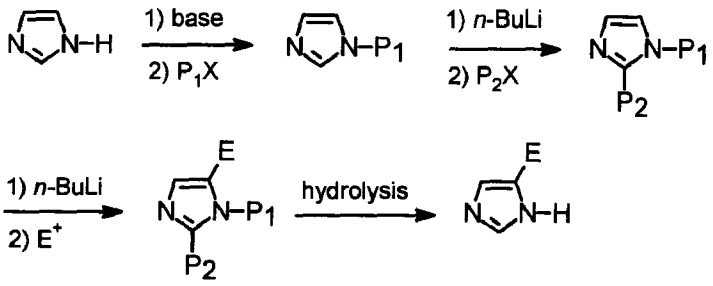
6.1 Introduction

Imidazole rings are incorporated in a great variety of molecules, many of which are of biological interest. Imidazole units not only are present in well known compounds such as histidine and histamines, adenine and guanine, and vitamin B12, they also occur in various pharmaceuticals, fungicides, and herbicides.[2] As a matter of fact four of the top twenty ethical pharmaceuticals prescribed in the US in 1994 contain either a simple imidazole ring (Tagamet) or the fused rings of benzimidazole (Losec, Prilosec) and purine (Zovirax).[3]

The two nitrogen atoms of imidazoles proper are equivalent due to a rapid 1,3-hydrogen shift, and the aromatic structure has an extremely high thermal stability (up to 590 °C).[4] It is remarkable how many different synthetic approaches have been developed for imidazoles since the parent compound was prepared nearly 140 years ago from glyoxal and ammonia.[5] Well known are the classical syntheses by Radziszewski,[6] Bredereck,[7] Weidenhagen,[8] and Marckwald.[9]

Currently, there is a growing interest in the development of reliable methods for

the synthesis of 4(5)-monosubstituted imidazoles **6.2**, especially in relation to the search for new histamine receptor agonists and antagonists. Some of the newer methods are based on the use of C5 lithiation reactions of a suitable 1,2-diprotected imidazole (Scheme 6.1).[10] In these approaches an efficient protection of both the N1- and C2 positions of the imidazole ring is necessary. Several protecting groups (P) have been tested by various research groups, such as for P_1 $-CH_2Ph$, $-CH_2OR$, $-CH(OR)_2$, $-SO_2Ar$, $-SO_2N(Me)_2$, $-CPh_3$, and $-SiMe_3$; for P_2 -SPh, $-SiMe_3$, and $-SiMe_2t$-Bu.

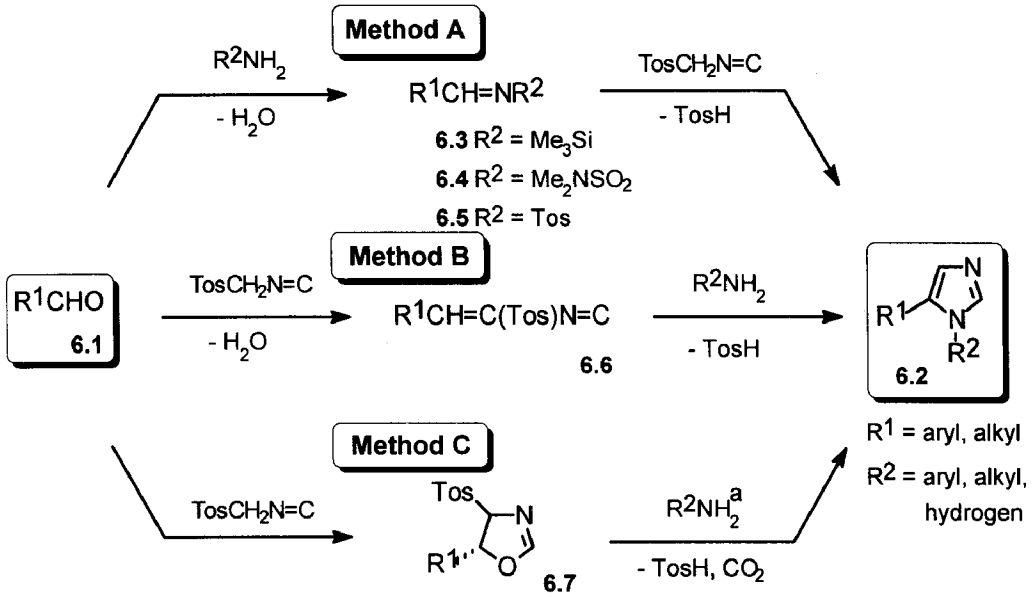


Scheme 6.1 : *Synthesis of 4(5)-Monosubstituted Imidazoles*

Beginning in 1972,[11] our research group has contributed to the synthesis of the imidazole ring system with a novel approach, in which the N1-C2 and C4-C5 bonds are formed by reaction of tosylmethyl isocyanides (TosMIC, and derivatives thereof) with various imino compounds.[12] Basically, this approach leads to 1,5-disubstituted imidazoles (Scheme 6.2, Methods A and B), or to 1,4,5-trisubstituted imidazoles when monosubstituted TosMIC derivatives are used.[13] Recently, Horne *et al.*[14] have extended this approach by the introduction of Method C (Scheme 6.2).

Each of the three methods of Scheme 6.2 can be, and has been, adapted to prepare 4(5)-monosubstituted imidazoles. First, in 1979, our research group has shown that Method B leads to 4(5)-phenylimidazole (**6.2**, R^1 = Ph, R^2 = H, 65 % yield) when the reaction is carried out with ammonia instead of primary aliphatic amines. The reaction with ammonia, however, was not pursued beyond this one example.[15]

Recently, Shih has shown that Method A also leads to 4(5)-monosubstituted imidazoles **6.2** (R^2 = H, 5 examples, 23-55 % yield) when the reaction is carried out with *N*-(trimethylsilyl)aldimines **6.3**.[16] The trimethylsilyl group of the *N*-(trimethylsilyl)-aldimines **6.3** provides a temporary protection group. Finally, Horne *et al.* have prepared a series of the same type of monosubstituted imidazoles **6.2** (R^2 = H) by reaction of oxazolines **6.7** with ammonia (Method C, 10 examples, 52-80 % yield).[14]



a) For R^2 = alkyl, Method C leads to 1,4-disubstituted imidazoles (instead of 1,5-disubstituted isomers)[14]

Scheme 6.2 : *Three Methods for Conversion of Aldehydes to 1,5-Disubstituted [a] or 4(5)-Monosubstituted Imidazoles* ***6.2*** *using TosMIC*

The intermediates of Methods B and C in the conversion of aldehydes **6.1** to 4(5)-monosubstituted imidazoles **6.2** (R^2 = H) are isolable compounds (**6.6** and **6.7**, respectively), which can be stored. The *N*-(trimethylsilyl)aldimines **6.3** of Method A, however, have been used only as *in situ* prepared transient intermediates.[16]

Although many methods are known already, still there is a need for efficient syntheses of 4(5)-monosubstituted imidazoles **6.2**. In this chapter, we will describe two methods for the conversion of aldehydes to imidazoles of type **6.2** by Method A that rely on the use of isolable and storable intermediates: *N*-(dimethylsulfamoyl)aldimines **6.4** and *N*-tosylaldimines **6.5**. The synthesis of intermediates **6.4** and **6.5** are discussed in Sections 6.2.1 and 6.2.2, respectively.

6.2 Synthesis of *N*-(Dimethylsulfamoyl)aldimines and *N*-Tosylaldimines

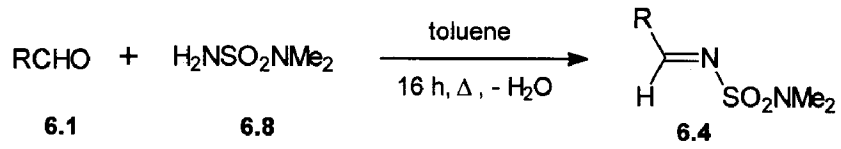
N-(Trimethylsilyl)aldimines **6.3** were already mentioned in Section 6.1. These aldimines do not belong to the category of isolable and storable, compounds. Our objective was, to use isolable, storable and readily obtainable aldimines as intermedi-

ates for the synthesis of 4(5)-monosubstituted imidazoles (**6.1**). Based on the experience of other research groups with *N*H protection of imidazoles,[10] we decided that the dimethylsulfamoyl group and the tosyl group were the best protecting groups for our purpose. In principle, aldimines derived from benzylamines[17] and *N*-tosylhydrazine[18] could also serve this purpose, however, it turned out that neither PhCH=N-CH_2Ph nor PhCH=NNHTos led to the desired imidazoles in the reaction of Method A (Scheme 6.2). We attribute this failure to the presence of acidic protons in these aldimines. The synthesis of ten *N*-(dimethylsulfamoyl)aldimines **6.4** is described in Section 6.2.1.

6.2.1 Synthesis of N-(Dimethylsulfamoyl)aldimines

The dimethylsulfamoyl group was introduced in 1984 by Chadwick and Ngochindo *et al.* as the very best *N*-H protector in 2- and 4-monoalkylation and 2,5-dialkylation studies of lithiated imidazoles (Scheme 6.1).[10b] Their experiences have recently been substantiated by Kudzma *et al.*[10f] and Vollinga *et al.*[10g] in an attractive synthesis of *inter alia* 4(5)-(ω-aminoalkyl)-1*H*-imidazoles from *N*-(dimethylsulfamoyl)imidazole. After completion of the substitution reactions at the imidazole ring, the dimethylsulfamoyl protection is readily removed with aqueous acid or base.[10b, 10d-g]

Much to our surprise *N*-(dimethylsulfamoyl)aldimines **6.4** have not been described earlier. We now report that the desired sulfamoylaldimines **6.4** are readily prepared by reaction of equimolar quantities of *N*-(dimethylsulfamoyl)amide[19] (**6.8**) and an aldehyde in refluxing toluene, under azeotropic removal of water. The aldimines **6.4** so obtained (Table 6.1, Scheme 6.3) are shelf-stable solids, with the exception of **6.4i**. Even compound **6.4i**, which is an oil, has been stored for more than 18 months at -20 °C without appreciable deterioration.

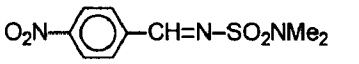
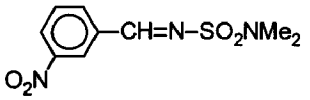
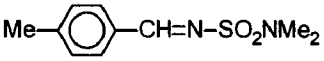
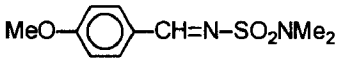
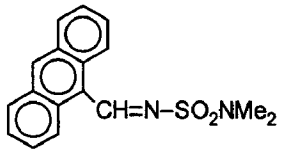
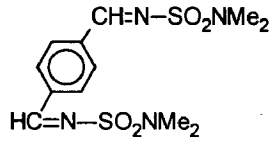
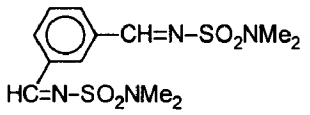
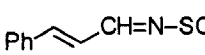


6.1 **6.8** **6.4**

Scheme 6.3 : *Synthesis of N-(Dimethylsulfamoyl)aldimines* **6.4**

The formation of imino compounds with the use of *N*-(dimethylsulfamoyl)amide (**6.8**) appears to be more facile than the corresponding reaction with ordinary sulfonamides, probably as a result of enhanced nucleophilicity of **6.8** (see Section 6.2.2).[20]

Table 6.1 : *N-(Dimethylsulfamoyl)aldimines* **6.4** *Prepared According to Scheme 6.3*

Entry	Product **6.4**		Yields[a] (%)	Mp (°C)
1	$PhCH{=}N{-}SO_2NMe_2$	**(6.4a)**	55	85-86
2		**(6.4b)**	70	178-179
3		**(6.4c)**	66	115-116
4		**(6.4d)**	51	98-99
5		**(6.4e)**	40	99-100
6		**(6.4f)**	68	164-165
7		**(6.4g)**	57[b]	212-213
8		**(6.4h)**	65[b]	208-209
9	$Me_2N{-}N{=}CH{-}CH{=}N{-}SO_2NMe_2$	**(6.4i)**	62	oil
10		**(6.4j)**	67[c]	87-88

(a) Isolated yield, after one crystallization. (b) Two equivalents of amine **6.8** were used, instead of one. (c) Reaction time 6h, instead of 16 h

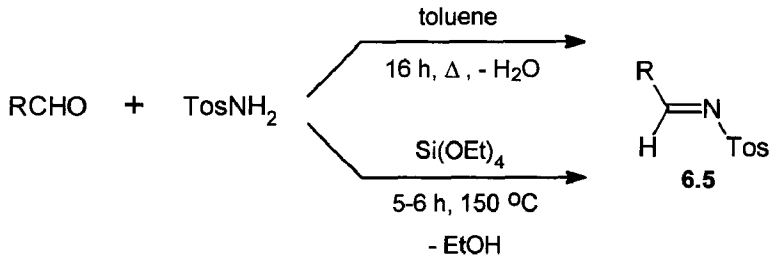
As conducted from ^{1}H and ^{13}C NMR, the aldimines **6.4** of Table 6.1 are formed as single stereoisomers to which the *E* configuration is assigned on the basis of NOESY experiments carried out with **6.4b** and **6.4f**.

The yield of entry 1 (55%) was not improved when the reaction time was prolonged from 16 to 32 h. Unsuccessful experiments were carried out, under the conditions given in Table 6.1, with aqueous glyoxal and with ethyl glyoxalate (50% in toluene). The corresponding reaction of 2-pyridinecarboxaldehyde only gave impure aldimine, which could not be purified.

In addition to their application in the synthesis of 4(5)-monosubstituted imidazoles **6.2**, the new *N*-(dimethylsulfamoyl)aldimines **6.4** may well become attractive substrates in (cyclo)addition reactions of the type where ordinary sulfonylimines have been utilized so far.[21f]

6.2.2 Synthesis of N-Tosylaldimines

In contrast to *N*-(dimethylsulfamoyl)aldimines **6.4**, *N*-tosylaldimines **6.5** are well known and several methods for the preparation of **6.5** have been reported. One of the simplest methods is the condensation of aldehydes and *p*-toluenesulfonamide under Dean-Stark conditions. However, the *N*-tosylaldimines **6.5** are obtained in rather low yields under these conditions. Therefore, these condensation reactions are normally performed in the presence of strong Lewis acids (such as $TiCl_4$).[21] This method, however, appears to be limited to aromatic aldehydes.[21] Other synthetic methods which have been used are: application of tellurium metal and chloramine-T,[22] rearrangement of oxime *O*-sulfinates,[23] reaction of an aldehyde with *N*-sulfinyl-*p*-toluenesulfonamide,[24] and condensation of aldehydes and *p*-toluenesulfonamide in the presence of tetraethyl orthosilicate.[25]



Scheme 6.4 : *Synthesis of N-Tosylaldimines*

For the preparation of the *N*-tosylaldimines **6.5** we have used two different methods. Compounds **6.5a**, **6.5b**, **6.5f**, **6.5g**, and **6.5k** were prepared by condensation of

aldehydes with *p*-toluenesulfonamide in refluxing toluene, under azeotropic removal of water.[26] Compounds **6.5d**, **6.5l**, and **6.5m** were prepared by heating the aldehyde and *p*-toluenesulfonamide in the presence of tetraethyl orthosilicate (Scheme 6.4).[25]

In Section 6.2.1, we already mentioned that under the same conditions (refluxing in toluene), *N*-(dimethylsulfamoyl)amide (**6.8**) reacts more readily than *p*-toluenesulphonamide. This difference in reactivity is clearly demonstrated in the reaction of *p*-methoxybenzaldehyde. Under the same conditions where 40 % of **6.4e** was obtained in reaction with **6.8** (Table 6.1, entry 5), no reaction took place between *p*-methoxybenzaldehyde and *p*-toluenesulfonamide after 16 h; not even when the reaction time in the latter case was extended to 65 h. This remarkable difference in results was found to be less pronounced in reaction of the more electrophilic benzaldehyde (**6.5a**: 37 %, 6 h reflux) and *p*-nitrobenzaldehyde (**6.5b**: 82 %, 2 d reflux).

In Section 6.3, the cycloaddition of TosMIC to the above mentioned sulfonylaldimines **6.4** and **6.5** will be described.

6.3 Synthesis of 4(5)-Monosubstituted Imidazoles

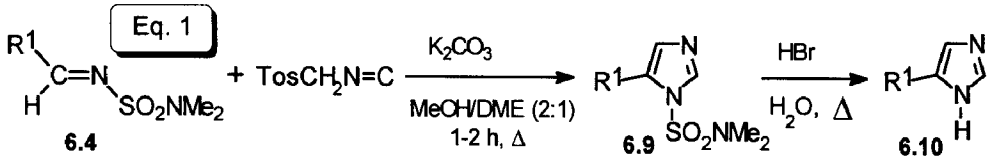
In Section 6.1, the importance of 4(5)-monosubstituted imidazoles was already indicated. With the development of the *N*-(dimethylsulfamoyl)aldimines **6.4** and the *N*-tosylaldimines **6.5** (Section 6.2), all ingredients for the planned synthesis of 4(5)-monosubstituted imidazoles **6.10** were available. First, in Section 6.3.1, we will describe the application of *N*-(dimethylsulfamoyl)aldimines **6.4** for this purpose. Then in Section 6.3.2, the use of *N*-tosylaldimines **6.5** will be dealt with.

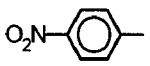
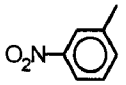
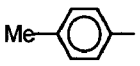
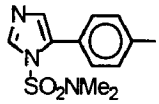
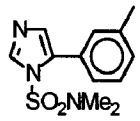
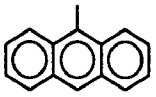
6.3.1 4(5)-Monosubstituted Imidazoles (6.1) from N-(Dimethylsulfamoyl)aldimines (6.4)

N-(Dimethylsulfamoyl)imidazoles (**6.9**) are readily prepared by base-induced cycloaddition of TosMIC and *N*-(dimethylsulfamoyl)aldimines **6.4** (Table 6.2, Eq. 1). The reaction proceeded smoothly by refluxing TosMIC and aldimines **6.4** in a mixture of MeOH/DME (2:1) for 1-2 h under basic conditions (K_2CO_3). Crystallization from isopropanol afforded the 1-(dimethylsulfamoyl)imidazoles **6.9** analytically pure.

The dimethylsulfamoyl group is readily removed from compounds **6.9** under acidic conditions, in refluxing 30 % HBr, to give the 4(5)-monosubstituted imidazoles **6.10**, which are isolated as HBr salts, in moderate to good yields (Table 6.2).[27]

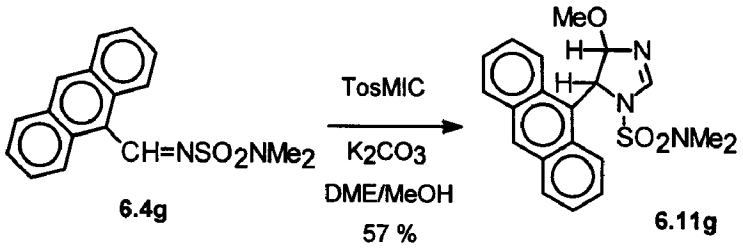
Table 6.2 : *1-(Dimethylsulfamoyl)imidazoles* ***6.9*** *and Corresponding 4(5)-Mono-substituted Imidazoles*[a] ***6.10*** *from N-(Dimethylsulfamoyl)aldimines (****6.4****) and TosMIC*



Entry	R^1 =	Compounds **6.9**	Yield (%)	mp (°C)	Compounds **6.10. n HBr**	Yield (%)	n =	mp (°C)
1		**6.9a**	65	117-118	**6.10a**	55	1	> 300
2		**6.9b**	68	192-193	**6.10b**	49	1	226-227
3		**6.9c**	67	95-96	**6.10c**	93	1	274-276
4		**6.9d**	55	113-114	**6.10d**	75	1	192-194
5		**6.9e**	69	156-157	**6.10e**[b]	94	2	> 300
6		**6.9f**	65	141-142	**6.10f**[b]	91	2	> 300
7		**6.11g**	57[c]	167-168				
8	(*E*)-PhCH=CH–	**6.9h**	72	105-106				
9	Me_2N-N=CH–	**6.9i**	70	oil				
10	(*E,E*)-$CH_3(CH{=}CH)_2$-	**6.9j**	50[d]	oil				

(a) Isolated as HBr salts. (b) The dimethylsulfamoyl group of substituent R^1 is removed simultaneously. (c) Under the conditions given in Eq. 1, only 5-(9-anthranyl)-1-(dimethylsulfamoyl)-4-methoxy-4*H*,5*H*-imidazoline (**6.11g**) was obtained, instead of imidazole **6.9g**. (d) Yield estimated by ^{1}H NMR.

In a few cases unexpected results were obtained. When the reaction of Eq. 1 was performed with *N*-(dimethylsulfamoyl)anthraldimine (**6.4g**, Table 6.2, entry 7) not the expected *N*-(dimethylsulfamoyl)imidazole **6.10g** was obtained, but 5-(9-anthranyl)-1-(dimethylsulfamoyl)-4-methoxy-4*H*,5*H*-imidazoline (**6.11g**, Scheme 6.5).



Scheme 6.5 : *Synthesis of 4-Methoxyimidazoline* ***6.11g***

As we will discuss below, imidazoline **6.11g** is a potential intermediate in the formation of **6.10g**. However, attempts to eliminate MeOH from **6.11g** to form **6.10g** in a reaction of isolated **6.11g** and *t*-BuOK in THF were unsuccessful. Also prolonged reaction times did not afford the desired imidazole **6.10g**. It is tempting to ascribe this anomalous result to the size of the 9-anthranyl substituent. Possibly, deprotonation of **6.11g** at C5 is hampered by insufficient resonance stabilization of the corresponding anion. To maximize the overlap between the lone pair at C5 and the aromatic substituent, a planar carbanion conformation must be realized in which the anthranyl moiety and the imidazolinyl ring are in the same plane. This is impossible (see Figure 3.2).

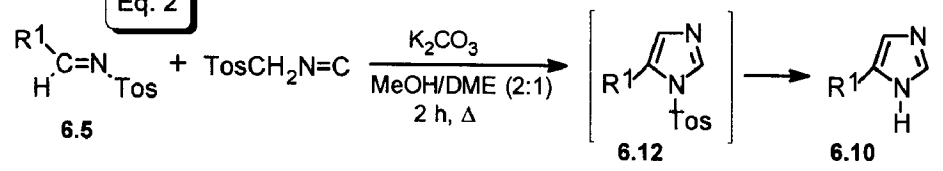
6.3.2 4(5)-Monosubstituted Imidazoles from N-Tosylaldimines

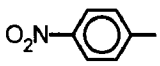
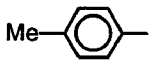
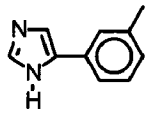
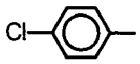
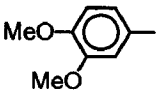
The method described above (in Section 6.3.1) to synthesize 4(5)-monosubstituted imidazoles is a two step process in which 1-(dimethylsulfamoyl)imidazoles **6.9** are first prepared and in which in a second step the dimethylsulfamoyl group is removed. We felt, however, that it ought to be possible also to develop a one step synthesis, with the use of *N*-tosylaldimines **6.5**. This assumption was based on several reports on deprotection of *N*-tosylimidazoles and *N*-tosylindoles. For the deprotection of *N*-tosyl substituted imidazoles several methods have been used. One of these methods is a basic hydrolysis using KOH in MeOH.[28] Another method, which has been used in the removal of a *N*-tosyl group of an indole is K_2CO_3 in $MeOH/H_2O$.[29] For the preparation of *N*-(dimethylsulfamoyl)imidazoles **6.9** we have

used K_2CO_3 in MeOH (Section 6.3.1). It seemed likely that under these conditions the *N*-tosyl group of imidazoles **6.12** would be removed to give imidazoles **6.10** in a one-pot synthesis.

Table 6.3 : *4(5)-Monosubstituted Imidazoles **6.10** from N-Tosylaldimines **6.5** and TosMIC*

Eq. 2



Entry	R^1 =	Compd.	Yield (%)	Mp (°C)/Lit.
1		**6.10a**	75	131-132/(128-129)
2		**6.10b**	62	210-212/(225)
3		**6.10d**	53	112-114/(116-117)
4		**6.10f**	a	
5	(*E*)-PhCH=CH–	**6.10h**	49	174-178/(181)
6		**6.10k**	55	140-143/(147)
7		**6.10l**	51	166-168
8		**6.10m**	6	115-116

a) Complex reaction mixture, **6.10f** not isolated

Reaction of TosMIC and *N*-tosylaldimines (**6.5**) with K_2CO_3 in MeOH gave, as expected, not the *N*-tosylimidazoles **6.12** but 4(5)-monosubstituted imidazoles **6.10**.

The tosyl group was removed indeed under the conditions used. The results are collected in Table 6.3. In the case of aldimine **6.5a**, 4(5)-phenylimidazole (**6.10a**) was obtained pure in a one-pot operation in 75 % yield (Table 6.3, entry 1). The yield of this reaction, as compared to the two step process discussed in Section 6.3.1 (Table 6.2, entry 1, overall yield 37 %) was twice as high.

6.3.3 *N-Methylated Side Products and Mechanistic Aspects*

A singlet at δ = 3.70 ppm in the ^{1}H NMR spectrum of crude **6.10a** was assigned to 1-methyl-4-phenylimidazole (**6.18a**, R^1 = Ph, Scheme 6.6), which was present in small amounts (< 5 % yield). Corresponding *N*-methylated side products were present more prominently in the products of entries 2, 3, 5, 6, and 8 (6-14 % yield). In these cases, the side products were isolated with the use of column chromatography. For entry 6, the structure of the side product was identified by X-ray analysis as 4-(*p*-chlorophenyl)-1-methylimidazole (**6.18k**; Figure 6.1). The structures of the other side products **6.18** were correlated by NOESY and the coupling constant of the aromatic protons of the 1,4 disubstituted imidazoles (J = 1.1-1.5 Hz for H-2,H-5).[30] Methylation of 4(5)-phenylimidazole (using dimethyl sulfate) has been reported to give a mixture of **6.18a** and 1-methyl-5-phenylimidazole (**6.19a**) in a ratio 5:1.[31]

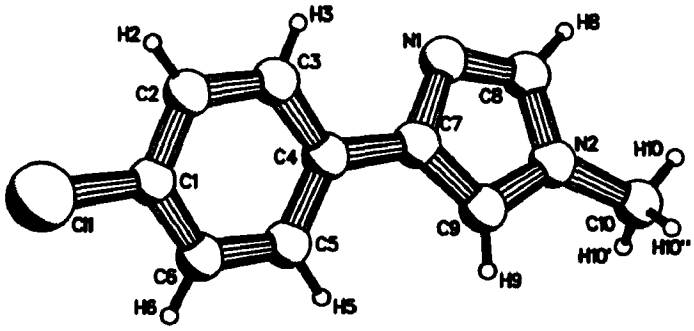
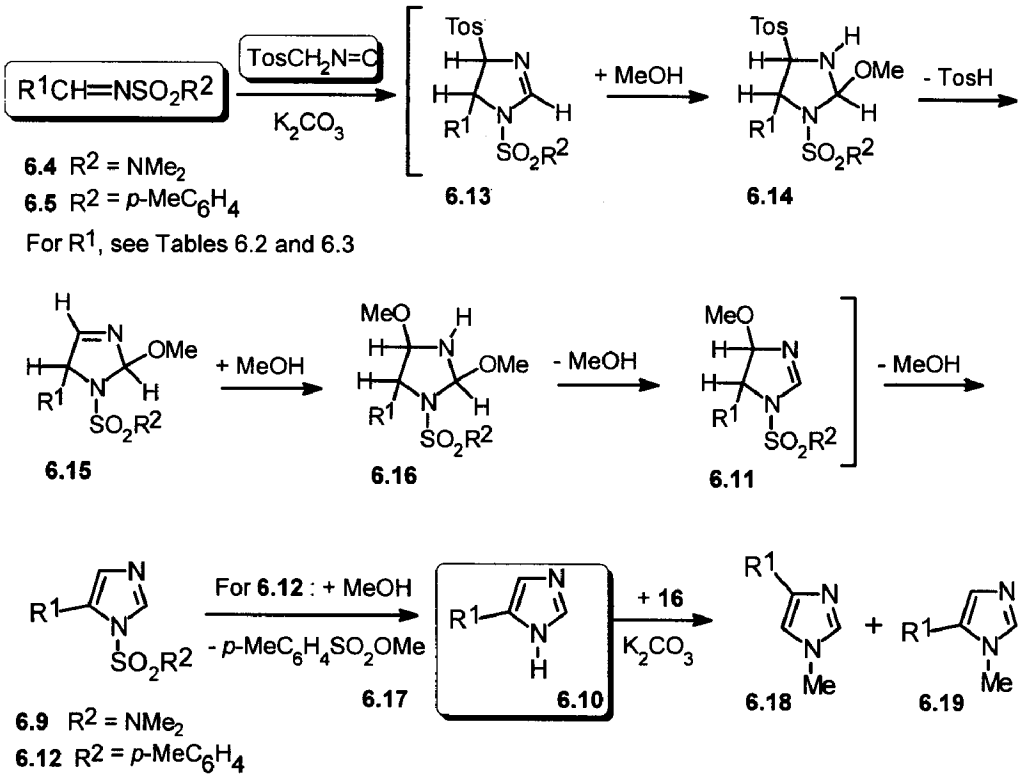


Figure 6.1 : *Pluto Representation of the Crystal Structure of 4-(p-Chlorophenyl)-1-methylimidazole (**6.18k**). Bond Lengths and Bond Angles are Listed in Table 6.4 (Experimental Section)*

When the reaction of Eq. 2 (for entry 2, Table 6.3) was repeated with EtOH, instead of MeOH, 1-ethyl-4-(*p*-nitrophenyl)imidazole was formed, under otherwise similar conditions, as the side product (25 % yield). Evidently, the cosolvent (MeOH

or EtOH) is responsible for the formation of the *N*-alkylated side products, such as **6.18b**, **6.18d**, **6.18h**, **6.18k**, and **6.18m**. However, it is unlikely that these side products are formed in a direct reaction between 4(5)-arylimidazoles **6.10** and the cosolvent. We propose that methyl *p*-toluenesulfonate (**6.17**), which is generated *in situ* during the formation of the imidazole ring, is the actual methylating agent (Scheme 6.6). With EtOH as cosolvent, *p*-$MeC_6H_4SO_2Et$ acts similarly as *N*-ethylating agent. This proposition is supported by the methylation of (*E*)-4-(2-phenylethenyl)imidazole (**6.10h**), in a separate experiment, to (*E*)-1-methyl-4-(2-phenylethenyl)imidazole (**6.18h**, R^1 = (*E*)-PhCH=CH, 69 % yield) with the use of methyl *p*-toluenesulfonate (**6.17**).



Scheme 6.6 : *A Rationale of the Formation of the 4(5)-Monosubstituted Imidazoles* ***6.10*** *and their N-Methyl Derivatives* ***6.18***

Most of the results discussed so far can be rationalized in Scheme 6.6. This scheme is modelled after a similar scheme that explains the various results of the reaction of TosMIC with aldehydes, described elsewhere.[12b] At first glance, Scheme

6.6 appears to ignore the virtues of Occam's razor, since the formation of compounds **6.9** and **6.12** could be explained more directly by assuming a base-induced elimination of *p*-toluenesulfinic acid (TosH) from **6.13**. Although we can not really exclude such an elimination of TosH in the synthesis of imidazoles (**6.13** → **6.9** or **6.12**), in the corresponding synthesis of oxazoles from TosMIC and aldehydes the roundabout way analogous to Scheme 6.6 seems more likely.[12b] In the latter case several oxazolines comparable to **6.15** and **6.11** (read O for R^2SO_2N) have been isolated and characterized.[12b]

We have identified two imidazolines of type **6.11** and **6.13**. The first one was already mentioned in Section 6.3.1 [5-(9-anthranyl)-1-(dimethyl-sulfamoyl)-4-methoxy-4*H*,5*H*-imidazoline (**6.11g**)]. The second imidazoline **6.13k** will be discussed below.

As was mentioned above, Scheme 6.6 also accounts for the formation of the side products **6.18** (and possibly **6.19**) in the reactions of Eq. 2. According to Scheme 6.6, 1-tosylimidazoles **6.12** may react intermolecularly with the cosolvent MeOH to give 4(5)-monosubstituted imidazoles **6.10**, together with methyl *p*-toluenesulfonate (**6.17**).[32] Alternatively, **6.17** could form intramolecularly from **6.15** (to give the 5*H* tautomer of **6.10** initially). Furthermore, the intramolecular elimination of **6.17** could precede aromatization in case of the intermediates **6.14** or **6.16** (always R^2 = *p*-MeC_6H_4).

Two unsuccessful attempts have been made to prevent, or to minimize, the formation of *N*-alkylated side products **6.18** (and possibly **6.19**) in the reaction of Eq. 2. First of all, the reaction of entry 6 (Table 6.3) was carried out with *t*-BuOH as cosolvent, instead of MeOH. It was hoped that *t*-butyl *p*-toluenesulfonate, if formed at all, would be a less effective *N*-alkylating agent. Under otherwise the same reaction conditions (*t*-BuOH/DME 2 : 1, reflux, 2 h), 5-(*p*-chlorophenyl)-1,4-ditosyl-4*H*,5*H*-imidazoline (**6.13k**, R^1 = *p*-ClC_6H_4, R^2 = *p*-MeC_6H_4) was obtained in 82 % yield. This experiment shows : (1) that no direct elimination of TosH (**6.13** → **6.12k**) is taking place, and (2) that no *p*-$MeC_6H_4SO_2O$*t*-Bu is formed (apparently none of the four possible routes discussed above for the formation of **6.17** with MeOH is working for *t*-BuOH). This result is consistent with the rationale given in Scheme 6.6. Under more drastic conditions (*t*-BuOH/DME 2 : 1, reflux, 20 h), 5-(*p*-chlorophenyl)-1-tosylimidazole (**6.12k**) was formed in a yield of 10 %. When the reaction of entry 5 (Table 6.3) was repeated with water instead of *t*-BuOH (reflux, 2 h) imidazoline **6.13k** was isolated again, although in lower yield (37 %).[33]

6.4 Conclusions

The overall yields of 4(5)-monosubstituted imidazoles **6.10** obtained by the methods given with Table 6.2 (Eq. 1) and Table 6.3 (Eq. 2) are comparable only in case of **6.10d** (41 % and 53 %, repectively). In the case of compounds **6.10a** and **b** the yields obtained with the method of Eq. 2 are twice as high as the overall yields obtained by Eq. 1. The approach of Eq. 2 takes two steps, one to convert the aldehyde with (cheap) *p*-toluenesulfonamide to *N*-tosylaldimines (**6.5**) and a second for the reaction with TosMIC to form **6.10**. A disadvantage of this method is the occasional formation of *N*-methylated side products **6.18** (in yields ranging from 5-14 %). In our hands, column chromatography was needed to remove the higher-yield side products. The approach of Eq. 1 is not hampered by the formation of side products. However, the removal of the dimethylsulfamoyl protection from **6.9** requires an additional step. Furthermore, *N*-(dimethylsulfamoyl)amide, the reagent for the syntheses of aldimines **6.4** also needs to be prepared from commercially available Me_2NSO_2Cl and ammonia. Nevertheless, the preparation of aldimines **6.4** proceeded in moderate to good yields.

6.5 Experimental Section (for General Remarks, see Chapter Two)

N-(Dimethylsulfamoyl)amide (**6.8**) was readily prepared on 0.15 mol-scale from commercial dimethylsulfamoyl chloride (Aldrich) and 30 % aqueous ammonia.[19] The precursor of **6.5i** was prepared from glyoxal and 1,1-dimethylhydrazine according to the literature procedure.[34] The other aldehydes are commercial products that have been used as received. All experiments were performed, except for the synthesis of **6.4**, in a dry nitrogen atmosphere. *N*-Tosylaldimines **6.5** have been reported previously: compounds **6.5a, 6.5b, 6.5f, 6.5g, and 6.5k** were easily prepared by condensation of an aldehyde with $TosNH_2$ in refluxing toluene without the use of a catalyst. In case of aldimines **6.5d**, **6.5l**, and **6.5m** the procedure of Love *et al.* was followed.[25] Aldehydes and $TosNH_2$ are commercial products, which have been used as received. 1,2-Dimethoxyethane (DME) was distilled from Na wire; EtOH (p.a.) and MeOH (p.a.) were dried over 3Å sieves.

6.5.1 *Synthesis of N-(Dimethylsulfamoyl)aldimines (6.4)*

General procedure. A solution of *N*-(dimethylsulfamoyl)amide (**6.8**) (10-11 mmole) and an aldehyde (10 mmole) in toluene (100 mL) was refluxed for 16 h in a Dean-Stark apparatus. The reaction mixture was concentrated and the residue was dissolved in CH_2Cl_2. After filtration through a short colomn of Al_2O_3 (CH_2Cl_2), the eluent was concentrated. Products **6.4a-6.4f** and **6.4j** were crystallized from isopropanol. Products **6.4g** and **6.4h** were obtained

in analytically pure form by cooling the reaction mixture to room temperature and collecting the precipated solid. Product **6.4i** was obtained analytically pure by distillative removal of impurities.

***N*-(Dimethylsulfamoyl)benzaldimine (6.4a) :**
White solid, 55 %, mp 85-86 °C; ^{1}H NMR ($CDCl_3$, 200 mHz): δ = 2.88 (s, 6H), 7.51-7.96 (m, 5H), 8.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 38.13 (q), 129.03 (d), 130.75 (d), 134.43 (s), 170.53 (d); MS (relative intensity, %): *m/z* = 28 (52.89), 44 (100.00), 51 (25.44), 77 (49.29), 104 (38.03), 106 (51.51), 108 (94.57), 212 (M^+, 54.42); HRMS: *m/z* calc. for $C_9H_{12}N_2O_2S$: 212.062, found 212.061; Anal. calcd. for $C_9H_{12}N_2O_2S$: C, 50.93; N, 13.20; H, 5.70; S, 15.10, found C, 50.86; N, 13.04; H, 5.72; S, 15.19.

***N*-(Dimethylsulfamoyl)-*p*-nitrobenzaldimine (6.4b) :**
Yellow solid, 70 %, 178-179 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.93 (s, 6H), 8.13 (d, *J* = 9.0 Hz, 2H), 8.37 (d, *J* = 8.8 Hz, 2H), 8.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 38.29 (q), 124.24 (d), 131.41 (d), 137.61 (s), 151.03 (s), 167.70 (d); MS (relative intensity, %): *m/z* = 28 (18.10), 43 (10.11), 44 (19.35), 76 (13.23), 108 (100), 151 (9.29); HRMS: *m/z* calc. for $C_9H_{11}N_3O_4S$: 257.047, found 257.047; Anal. calc. for $C_9H_{11}N_3O_4S$: C, 42.02; N, 16.31; H, 4.31; S, 12.46, found C, 42.15; N, 16.08; H, 4.56; S, 12.24.

***N*-(Dimethylsulfamoyl)-*m*-nitrobenzaldimine (6.4c) :**
Pale yellow solid, 66 %, mp 115-116 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.92 (s, 6H), 7.74 (t, *J* = 8.1Hz, 1H), 8.25 (d, *J* = 7.7 Hz, 1H), 8.44 (d, *J* = 8.1 Hz, 1H) 8.80 (s, 1H), 8.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 38.30 (q), 124.89 (d), 128.35 (d), 130.41 (d), 134.10 (s), 136.11 (d) 167.80 (d); MS (relative intensity, %): *m/z* = 28 (30.10), 42 (13.18), 43 (15.51), 44 (27.64), 76 (11.89), 108 (100), 151 (12.14), 257 (M^+, 21.30); HRMS: *m/z* calc. for $C_9H_{11}N_3O_4S$: 257.047, found 257.047; Anal. calc. for $C_9H_{11}N_3O_4S$: C, 42.02; N, 16.33 ; H, 4.31; S, 12.46, found C, 41.49; N, 15.86; H, 4.32; S, 12.32.

***N*-(Dimethylsulfamoyl)-*p*-tolualdimine (6.4d) :**
White solid, 51 %, mp 98-99 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.45 (s, 3H), 2.85 (s, 6H), 7.32 (d, *J* = 8.1 Hz, 2H,), 7.83 (d, *J* = 8.1 Hz, 2H), 8.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 21.99 (q), 38.14 (q), 129.88 (s), 129.94 (d), 130.99 (d), 145.91 (s), 170.50 (d); MS (relative intensity, %): *m/z* = 28 (50.85), 39 (13.18), 42 (20.06), 44 (100), 65 (21.58), 91 (44.51), 108 (52.23), 118 (60.49), 119 (45.04), 226 (M^+, 46.42); HRMS: *m/z* calc. for $C_{10}H_{14}N_2O_2S$: 226.078, found 226.078; Anal. calc. for $C_{10}H_{14}N_2O_2S$: C, 53.08; N, 12.38; H, 6.24; S, 14.17, found C, 52.81; N, 12.30; H, 6.22; S, 14.20.

***N*-(Dimethylsulfamoyl)-*p*-methoxybenzaldimine (6.4e) :**
White solid, 40 %, mp 99-100 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.86 (s, 6H), 3.90 (s, 3H), 7.00 (d, *J* = 9.1 Hz, 2H), 7.90 (d, *J* = 8.8 Hz, 2H), 8.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 38.29 (q), 55.55 (q), 114.54 (d), 125.14 (s), 133.07 (d), 164.79 (s), 169.58 (d); MS (relative intensity, %): *m/z* = 28 (12.88), 42 (23.38), 44 (60.79), 64 (18.52), 77 (34.46), 92 (32.93), 107 (23.90), 108 (27.44), 134 (100), 135 (86.07), 242 (M^+, 39.53); HRMS: *m/z* calc. for $C_{10}H_{14}N_2O_3S$: 242.073, found 242.073; Anal. calc. for $C_{10}H_{14}N_2O_3S$: C,49.57; N, 11.57; H, 5.83; S, 13.21, found C, 49.37; N, 11.44; H, 5.91; S, 13.29.

N-(Dimethylsulfamoyl)-9-anthraldimine (6.4f) :
Orange solid, 68 %, mp 164-165 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.98 (s, 6H), 7.55-7.61 (m, 2H), 7.67-7.73 (m 2H), 8.09 (d, *J* = 8.8 Hz, 2H), 8.72 (s, 1H), 8.94 (d, *J* = 8.4 Hz, 2H), 10.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 38.48 (q), 124.19 (d), 125.86 (d), 129.31 (d), 129.62 (d), 131.12 (s), 132.71 (s), 135.77 (d), 168.83 (d); MS (relative intensity, %): *m/z* = 28 (78.35), 32 (16.62), 176 (21.28), 177 (24.64), 180 (31.85), 182 (10.06), 203 (68.59), 204 (100), 312 (M^+, 14.58); HRMS: *m/z* calc. for $C_{17}H_{16}N_2O_2S$: 312.093, found 312.093; Anal. calc. for $C_{17}H_{16}N_2O_2S$: C, 65.36; N, 8.97; H, 5.16; S, 10.26, found C, 65.11; N, 8.83; H, 5.17; S, 10.31.

N,N'-Bis-(dimethylsulfamoyl)terephthaldimine (6.4g) :
Pale yellow solid, 57 %, 212 -213 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.93 (s, 6H), 8.09 (s, 4H), 8.96 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 38.21 (q), 130.98 (d), 137.20 (s), 168.64 (d); MS (relative intensity, %): *m/z* = 28 (100), 32 (23.12), 44 (23.79), 108 (41.73), 180 (6.71), 346 (M^+, 4.39); HRMS: *m/z* calc. for $C_{12}H_{18}N_4O_4S_2$: 346.077, found 346.077; Anal. calc. for $C_{12}H_{18}N_4O_4S_2$: C, 41.61; N, 16.17; H, 5.24; S, 18.51, found C, 41.25; N, 15.77; H, 5.30; S, 18.11.

N,N'-Bis-(dimethylsulfamoyl)isophthaldimine (6.4h) :
Off-white solid, 65 %, mp 208-209 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.93 (s, 6H), 7.71 (t, *J*= 7.9 Hz, 1H), 8.19 (d, *J* = 7.9 Hz, 2H), 8.53 (s, 1H), 8.99 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 38.52 (q), 130.29 (d), 132.54 (d), 133.81 (s), 135.98 (d), 169.02 (d); MS (relative intensity, %): *m/z* = 28 (15.6), 42(19.3), 44 (86.5), 76 (11.5), 108 (100), 212 (24.8), 239 (53.1), 346 (M^+, 0.1); HRMS was not observed; Anal. calc. for $C_{12}H_{18}N_4O_4S_2$: C, 41.61; N, 16.17; H, 5.24; S, 18.51, found C, 41.25; N, 15.77; H, 5.30; S, 18.11.

N-(Dimethylamino)-N'-(dimethylsulfamoyl)-1,4-diaza-1,3-butadiene (6.4i) :
Red-brown oil, 62 %; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.76 (s, 6H), 3.20 (s, 6H), 6.82 (d, *J* = 8.3 Hz, 1H), 8.46 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 38.34 (q), 124.55 (d), 169.75 (d); MS (relative intensity, %): *m/z* = 28 (31.59), 42 (55.08), 43 (27.54), 44 (100), 45 (45.25), 58 (17.17), 71 (23.08), 83 (13.91), 98 (64.89), 108 (22.42), 205 (17.45), 206 (M^+, 1.48); HRMS: *m/z* calc. for $C_6H_{14}N_4O_2S$: 206.84, found 206.84; Anal. calc. for $C_6H_{14}N_4O_2S$: C, 34.94; N, 27.16; H, 6.84; S, 15.54, found C, 34.93; N, 27.07; H, 6.76; S, 15.38.

N-(Dimethylsulfamoyl)cinnamaldimine (6.4j) :
Pale yellow solid, 67 %, mp 87-88 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.82 (s, 6H), 6.93-7.02 (dd, *J* = 9.5 Hz, *J* = 9.5 Hz, 1H), 7.41-7.57 (m, 6H), 8.62 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 38.11 (q), 124.40 (d), 128.30 (d), 129.00 (d), 131.25 (d), 134.08 (s), 152.65 (d), 171.38 (d); MS (relative intensity, %): *m/z* = 28 (37.05), 32 (8.22), 44 (11.42) 77 (11.44), 103 (14.51), 108 (13.44), 130 (100), 238 (M^+, 7.39); m/z; HRMS: *m/z* calc. for $C_{11}H_{14}N_2O_2S$: 238.078, found 238.078; Anal. calc. for $C_{11}H_{14}N_2O_2S$: C, 55.44; N, 11.76; H, 5.93; S, 13.43, found C, 55.23; N, 11.53; H,5.90; S,13.40.

6.5.2 Synthesis of 1-(dimethylsulfamoyl)imidazoles (6.9)

1-(Dimethylsulfamoyl)-5-phenylimidazole (6.9a) (Typical Procedure) :
A mixture of TosMIC (0.20 g, 1.0 mmol), *N*-(dimethylsulfamoyl)benzaldimine (**6.4a**, 0.21 g, 1.0

mmol), and K_2CO_3 (0.15 g, 1.1 mmol) in MeOH/DME 2:1 (30 mL) was refluxed for 90 min. After cooling, the reaction mixture was quenched with water (10 mL) and stirred for 5 min at room temperature. The mixture was poured in 50 mL of water and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. One crystallization from isopropanol gave analytically pure **6.9a** as a white solid (0.16 g, 65 %): mp 117-118 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.43 (s, 6H), 7.03 (br s, 1H), 7.41-7.52 (m, 5H), 8.01 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 37.19 (q), 128.04 (d), 128.07 (s), 129.15 (d), 130.63 (d), 130.76 (d), 131.76 (s), 139.93 (d); MS (relative intensity, %): *m/z* = 28 (54.3), 42 (19.7), 57 (18.7), 89 (63.0), 108 (57.8), 116 (25.5), 143 (100), 251 (M^+, 80.1); HRMS: *m/z* calc. for $C_{11}H_{13}N_3O_2S$: 251.073; found 251.073; Anal calc. for $C_{11}H_{13}N_3O_2S$: C, 52.57; N, 16.72; H, 5.21; S, 12.75; found C, 51.94; N, 16.50; H, 5.21; S, 12.56.

1-(Dimethylsulfamoyl)-5-(*p*-nitrophenyl)imidazole (6.9b) :
Following the procedure described for **6.9a**, *N*-(dimethylsulfamoyl)-*p*-nitrobenzaldimine (**6.4b**, 0.26 g, 1.0 mmol) gave, after crystallization from isopropanol, analytically pure **6.9b** as a yellow solid (0.20 g, 68%): mp 192-193 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.56 (s, 6H), 7.17 (br s, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 8.10 (br s, 1H), 8.30 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 37.69 (q), 123.35 (d), 130.12 (s), 131.23 (d), 132.50 (d), 134.89 (s), 141.04 (d), 148.05 (s); MS (relative intensity, %): *m/z* = 28 (9.70), 42 (9.44), 44 (19.64), 88 (12.80), 108 (100), 296 (M^+, 35.24); HRMS: *m/z* calc. for $C_{11}H_{12}N_4O_4S$: 296.058; found 296.058; Anal. calc. for $C_{11}H_{12}N_4O_4S$: C, 44.59; N, 18.91; H, 4.08; S, 10.82; found C, 44.68; N, 18.24; H, 4.30; S, 10.41.

1-(Dimethylsulfamoyl)-5-(*m*-nitrophenyl)imidazole (6.9c) :
Following the procedure described for **6.9a**, *N*-(dimethylsulfamoyl)-*m*-nitrobenzaldimine (**6.4c**, 0.26 g, 1.0 mmol) gave, after crystallization from isopropanol, analytically pure **6.9c** as an off-white solid (0.20 g, 67 %): mp 95-96 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.58 (s, 6H), 7.16 (br s, 1H), 7.63 (dd, *J* = 7.6 Hz, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 8.09 (br s, 1H), 8.30 (d, *J* = 8.1 Hz, 1H), 8.37 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75.4 MHz): δ = 37.87 (q), 124.09 (d), 125.29 (d), 129.41 (d), 130.01 (s), 130.32 (s), 132.41 (d), 136.83 (d), 140.81 (d), 148.11 (s); MS (relative intensity, %): *m/z* = 28 (34.91), 42 (11.34), 44(22.61), 88 (10.18), 108 (100), 296 (M^+, 18.91); HRMS: *m/z* calc. for $C_{11}H_{12}N_4O_4S$: 296.058; found 296.058; Anal. calc. for $C_{11}H_{12}N_4O_4S$: C, 44.59; N, 18.91; H, 4.08; S, 10.82; found C, 44.23; N, 18.75; H, 4.11; S, 10.61.

1-(Dimethylsulfamoyl)-5-*p*--tolylimidazole (6.9d) :
Following the procedure described for **6.9a**, *N*-(dimethylsulfamoyl)-*p*-tolualdimine (**6.4d**, 0.22 g, 1.0 mmol) gave, after crystallization from isopropanol, analytically pure **6.9d** as a white solid (0.15 g, 55%): mp 113-114 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.40 (s, 3H), 2.46 (s, 6H), 7.01 (br s, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.40 (*d*, J = 7.8 Hz, 2H), 8.04 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 21.22 (q), 37.26 (q), 125.11 (s), 128.72 (d), 130.53 (d), 130.66 (d), 131.88 (d), 139.20 (s), 139.80 (s); MS (relative intensity, %): *m/z* = 28 (9.35), 42 (9.60), 44 (11.05), 57 (10.94), 77 (14.41), 103 (41.08), 108 (13.03), 130 (15.16), 157 (100), 158 (21.03), 265 (M^+, 41.15); HRMS: *m/z* calc. for $C_{12}H_{15}N_3O_2S$: 265.088; found 265.088; Anal. calc. for $C_{11}H_{12}N_4O_4S$: C, 54.32; N,15.85; H, 5.70; S, 12.06; found C, 54.28; N, 15.70; H, 5.97; S, 12.10.

1,4-Di-[1-(dimethylsulfamoyl)-5-imidazolyl]benzene (6.9e) :
A solution TosMIC (0.39 g, 2.0 mmol), *N,N* -bis-(dimethylsulfamoyl)terephthaldialdimine (**6.4e**, 0.35 g, 1.0 mmol), and K_2CO_3 (0.29 g, 2.1 mmol) in MeOH/DME 2:1 (30 mL) was refluxed for 90 min. The reaction mixture was quenched with water (10 mL) and stirred for 5 min at room temperature. The precipated solid was collected and washed several times with portions of hexane (20 mL) to give analytically pure **6.9e** as a white solid (0.29 g, 69%): mp 156-157 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.56 (s, 12H), 7.09 (d, *J* = 1.0 Hz, 2H), 7.76 (s, 4H), 8.05 (d, *J* = 1.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 37.54 (q), 129.12 (d), 130.26 (d), 131.24 (s), 131.28 (d), 140.06 (s); MS (relative intensity, %): *m/z* = 28 (13.33), 42 (14.35), 44 (24.52), 64 (11.21), 108 (61.86), 127 (14.17), 154 (11.21), 181 (10.62), 209 (19.33), 316 (100), 424 (M^+, 56.31); HRMS: *m/z* calc. for $C_{16}H_{20}N_6O_4S_2$: 424.099; found 424.099; Anal. calc. for $C_{16}H_{20}N_6O_4S_2$: C, 45.27; N, 19.81; H, 4.75; S, 15.08; found C, 45.14; N, 19.73; H, 4.75; S, 15.08.

1,3-Di-[1-(dimethylsulfamoyl)-5-imidazolyl]benzene (6.9f) :
Following the procedure described for **6.9e**, *N,N* -bis-(dimethylsulfamoyl)isophthaldialdimine (**2f**, 0.35 g, 1.0 mmol) gave analytically pure **6.9f** as an off-white solid (0.27 g, 65%): mp 141-142 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.56 (s, 12H), 7.09 (br s, 2H), 7.45-7.65 (m, 4H), 8.05 (br s, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 37.53 (q), 127.82 (d), 128.29 (s), 131.11 (d), 131.34 (d), 132.54 (d), 132.57 (d), 139.97 (s); MS (relative intensity, %): *m/z* = 28 (15.10), 42 (16.1), 44 (22.90), 64 (11.30), 108 (59.60), 127 (14.20), 154 (13.60), 209 (21.10), 316 (53.50), 424 (M^+, 100); HRMS: *m/z* calc. for $C_{16}H_{20}N_6O_4S_2$: 424.099, found 424.099; Anal. calc. for $C_{16}H_{20}N_6O_4S_2$: C, 45.27; N, 19.81; H, 4.75; S, 15.08; found C, 45.20; N, 19.57; H, 4.78; S, 14.83.

5-(9-Anthranyl)-1-(dimethylsulfamoyl)-4-methoxy-4*H*,5*H*-imidazoline (6.11g) :
TosMIC (0.70 g, 3.6 mmol), *N*-(dimethylsulfamoyl)-9-anthraldimine (**6.4g**, 0.94 g, 3.0 mmol), and K_2CO_3 (0.99 g, 7.2 mmol) were refluxed in a mixture of MeOH/DME 2 :1 (30 mL) for 2 h. After cooling, the reaction mixture was quenched with water (50 mL) and the mixture was stirred for 10 min at room temperature. The mixture was extracted with CH_2Cl_2 (2 X 50 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was crystallized from EtOH (96 %) to give **6.11g** as orange crystals (1.70 g, 57 %). Recrystallization of **6.11g** from the same solvent gave pale yellow crystals: mp. 167-168 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.68 (s, 6H), 3.60 (s, 3H), 5.76 (d, *J* = 6.6 Hz, 1H), 6.25 (d, *J* = 6.6 Hz, 1H), 7.47-7.79 (m, 6H), 8.00-8.11 (m, 2H), 8.51-8.57 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 36.20 (q), 56.37 (d), 62.32 (d), 106.82 (d), 123.00 (d), 123.47 (d), 125.06 (d), 125.29 (d), 126.43 (d), 127.12 (s), 127.47 (d), 129.07 (d), 129.20 (s), 129.38 (d), 129.88 (d), 131.21 (s), 131.36 (s), 131.56 (s), 152.51 (d); MS (relative intensity, %): *m/z* = 28 (60.81), 32 (13.69), 45 (33.46), 204 (10.81), 275 (100), 216 (86.89), 351 (6.66), 383 (M^+, 5.34); HRMS: *m/z* calc. for $C_{20}H_{21}N_3O_3S$: 383.130, found 383.130; Anal calc. for $C_{20}H_{21}N_3O_3S$: C, 62.64; N, 10.96; H, 5.52; S, 8.34; found C, 62.88; N, 10.81; H, 5.49; S, 7.93.
Attempts to prepare the corresponding imidazole **6.9g** by elimination of MeOH from **6.11g** using *t*-BuOK in THF remained inconclusive.

(*E*)-1-(Dimethylsulfamoyl)-5-(2-phenylethenyl)imidazole (6.9h) :
Following the procedure described for **6.9a**, *N*-(dimethylsulfamoyl)cinnamaldimine (**6.4h**, 0.48

g, 2.0 mmol) gave, after crystallization from isopropanol, analytically pure **6.9h** as white crystals (0.40 g, 72 %): mp 105-106 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.99 (s, 6H), 7.14 (d, *J* = 16.5 Hz, 1H), 7.43-7.63 (m, 7H), 8.08 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 38.05 (q), 114.03 (d), 126.44 (d), 128.03 (d), 128.29 (d), 128.71 (d), 131.12 (s), 131.83 (d), 136.04 (s), 138.74 (d); MS (relative intensity, %): *m/z* = 28 (42.32), 32 (9.47), 115 (5.98), 143 (19.49), 170 (5.67), 277 (M^+, 100); HRMS: *m/z* calc. for $C_{13}H_{15}N_3O_2S$: 277.088, found 277.088; Anal. calc. for $C_{13}H_{15}N_3O_2S$: C, 56.30; N, 15.16; H, 5.46; S, 11.54; found C, 56.24; N, 15.00; H, 5.30; S, 11.74.

1-(Dimethylsulfamoyl)imidazole-2-carboxaldehyde dimethylhydrazone (6.9i) :
Following the procedure described for **6.9a**, *N*-(dimethylamino)-*N'*-(dimethylsulfamoyl)-1,4-diaza-1,3-butadiene (**6.4i**, 0.21 g, 1.0 mmol) gave, after workup, **6.9i** in almost pure form as a red brown oil (1.71 g, 70 %): ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.83 (s, 6H), 2.98 (s, 6H), 7.32 (m, 2H), 7.85 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 37.95 (q), 42.19 (q), 119.56 (d), 126.98 (d), 130.25 (s), 137.47 (d); MS (relative intensity, %): *m/z* = 28 (50.35), 42 (60.10), 44 (99.40), 52 (11.14), 67 (26.17), 94 (57.77), 110 (42.06), 137 (47.84), 245 (M^+, 100); HRMS calc.$C_8H_{15}N_5O_2S$: 245.095, found 245.095.

(*E, E*)-1-(Dimethylsulfamoyl)-5-(1,3-pentadienyl)imidazole (6.9j) :
Following the procedure described for **6.9a**, (*E, E*)-*N*-(dimethylsulfamoyl)-2,4-hexadienaldimine (**6.4j**, 0.20g, 1.0 mmol) gave, after column chromatography (silica gel, Et_2O), **6.9j** as a crude brown oil (0.12 g, ca. 50 %). Further attempts at purification by crystallization and distillation were unsuccessful. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.83 (d, *J* = 6.8 Hz, 3H), 2.85 (s, 6H), 5.82-5.93 (m, 1H), 6.14-6.30 (m, 1H), 6.61-6.64 (m, 2H), 7.20 (br s, 1H), 7.88 (br s, 1H).

6.5.3 Synthesis of 4(5)-Monosubstituted Imidazoles (6.10)

4(5)-Phenylimidazole hydrobromide (6.10a.HBr) (Typical Procedure) :
Following the conditions of Vollinga *et al.*,[11g] **6.9a** (0.76 g, 3.03 mmol) was dissolved in 30% aqueous HBr and heated under reflux for 90 min. The mixture was cooled and concentrated under vacuum. The residue was dissolved in absolute EtOH (50 mL), heated under reflux for 30 min, and concentrated under reduced pressure. The remaining yellow solid was washed with acetone to give almost pure **6.10a.HBr** as an off-white solid (0.37 g, 55%): mp > 300 °C; ^{1}H NMR (DMSO.d_6, 200 MHz): δ 7.53-8.31 (m, 5H), 9.16 (m, 2H); ^{13}C NMR (DMSO.d_6, 75.4 MHz): δ =116.38 (d), 122.93 (d), 125.69 (d), 128.09 (s), 130.35 (d), 132.15 (s), 135.65 (d); Anal. calc. for $C_9H_9N_2Br$: C, 48.03; N, 12.45; H, 4.03; Br, 35.50; found C, 47.16; N, 12.11; H, 3.84; Br, 34.86 (the sample of **6.10.HBr** used for elemental analysis was not subjected to further purification).[35]

4(5)-(*p*-Nitrophenyl)imidazole hydrobromide (6.10b.HBr) :
From **6.9b** (0.20 g, 0.7 mmol) by 16 h of reflux with 30 % HBr. After workup the remaining yellow solid was washed with acetone to give pure **6.10b.HBr** as a white solid (95 mg, 49%): mp 226-227 °C. ^{1}H NMR (DMSO.d_6, 200 MHz): δ = 8.07 (d, *J* = 8.8 Hz, 2H), 8.35 (d, *J* = 8.8 Hz, 2H), 8.34 (br s, 1H), 9.06 (br s, 1H); ^{13}C NMR (DMSO.d_6, 75.4 MHz): δ = 118.04 (d), 124.46 (d), 126.02 (d), 131.67 (s), 134.39 (s), 136.54 (d), 146.93 (s); MS (relative intensity,

%): *m/z* = 28 (11.86), 50 (3.21), 62 (5.90), 63 (9.87), 80 (18.47), 82 (19.23), 89 (34.86), 116 (42.75), 143 (36.37), 189 (M^+, 100); HRMS: *m/z* calc. for $C_9H_7N_3O_2$: 189.054, found 189.054.[35]

4(5)-(*m*-Nitrophenyl)imidazole hydrobromide (6.10c.HBr) :
From **6.9c** (0.29 g, 1.0 mmol) by 2 h of reflux with 30% HBr. After workup the remaining yellow solid was washed with acetone to give pure **6.10c.HBr** as a white solid (0.25 g, 93%): mp 274-276 °C. ^{1}H NMR (DMSO.d_6, 200 MHz): δ = 7.67-7.72 (dd, *J* = 8.1 Hz, *J* = 8.1, 1H), 8.16 (d, *J* = 7.0 Hz, 2H), 8.30 (br s, 1H), 8.60 (br s, 1H), 9.17 (br s, 1H); ^{13}C NMR (DMSO.d_6, 75.4 MHz): δ = 117.43 (d), 120.01 (d), 123.72 (d), 129.08 (s), 131.06 (d), 131.75 (d), 132.21 (s), 136.15 (d), 148.58 (s); MS (relative intensity, %): *m/z* = 28 (57.83), 32 (12.59), 63 (8.25), 80 (20.90), 82 (19.79), 89 (29.13), 116 (36.95), 143 (32.94), 189 (M^+, 100), 191 (10.96); HRMS: *m/z* calc. for $C_9H_7N_3O_2$:189.054, found 189.054.[35]

4(5)-(*p*-Tolyl)imidazole hydrobromide (6.10d.HBr) :
From **6.9d** (0.25 g, 1.0 mmol) by 16 h of reflux with 30 % HBr. After workup the remaining yellow solid was washed with acetone to give pure **6.10d.HBr** as a white solid (0.17 g, 75%): mp 192-194 °C. ^{1}H NMR (DMSO.d_6, 200 MHz): δ = 2.33 (s, 3H), 7.32 (d, *J* = 7.8, 2H), 7.69 (d, *J* = 8.3 Hz, 2H), 8.10 (s, 1H), 9.17 (s, 1H); ^{13}C NMR (DMSO.d_6, 75.4 MHz): δ = 20.85 (q), 124.03 (s), 114.89 (d), 125.22 (s), 129.73 (s), 132.64 (d), 134.93 (d), 138.86 (s); MS (relative intensity, %): *m/z* = 28 (5.02), 41 (4.59), 51 (6.12), 63 (4.90), 65 (3.31), 77 (10.81), 79 (6.18), 80 (13.38), 82 (12.92), 103 (14.70), 130 (23.58), 157 (28.66), 158 (M^+, 100); HRMS: *m/z* calc. for $C_{10}H_{10}N_2$: 158.084, found 158.084.[35]

1,4-Di[(4(5)-imidazolyl)benzene dihydrobromide (6.10e.2HBr) :
From **6.9e** (0.54 g, 2.0 mmol) by 16 h of reflux with 30 % HBr. After workup the remaining yellow solid was washed with acetone to give almost pure **6.10e.HBr** as a white solid (0.33 g, 94 %): mp > 300 °C. ^{1}H NMR (DMSO.d_6. 200 MHz): δ = 7.99 (s, 4 H), 8.30 (d, *J* = 1.2 Hz, 2H), 9.28 (d, *J* = 1.5 Hz, 2H); MS (relative intensity, %): *m/z* = 28 (72.71), 32 (15.97), 79 (13.69), 80 (40.42), 82 (38.98), 155(8.73), 171 (17.08), 211 (M^+, 100); HRMS: *m/z* calc. for $C_{12}H_{10}N_4$: 210.091, found 210.091.

1,3-Di[4(5)-imidazolyl]benzene dihydrobromide (6.10f.2HBr) :
From **6.9f** (0.42 g, 1.0 mmol) by 16 h of reflux with 30 % HBr. After workup the remaining yellow solid was washed with acetone to give pure **6.10f.HBr** as a white solid (0.35 g, 91%): mp > 300 °C; ^{1}H NMR (DMSO.d_6, 200 MHz): δ = 7.70 (dd, *J* = 7.8 Hz, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 7.0 Hz, 2H), 8.30 (br s, 2H), 8.44 (br s, 1H), 9.31 (d, *J* = 1.0 Hz, 2H); ^{13}C NMR (DMSO.d_6, 75.4 MHz): δ = 116.41 (d), 123.01 (d), 125.75 (d), 128.11 (s), 130.41 (d), 132.18 (s), 135.69 (d); MS (relative intensity, %): *m/z* = 28 (50.61), 32 (12.62), 79 (20.02), 80 (46.60), 81 (18.45), 82 (49.17), 155 (10.19), 210 (M^+, 100.00); HRMS: *m/z* calc. for $C_{12}H_{10}N_4$: 210.091, found 210.091.

4(5)-(Phenyl)imidazole (6.10a) (Typical Procedure) :
A mixture of TosMIC (0.64 g, 3.3 mmol), *N*-tosylbenzaldimine (**6.5a**, 0.78 g, 3.0 mmol), and K_2CO_3 (1.24 g, 9.0 mmol) in MeOH/DME 2:1 (30 mL) was refluxed for 90 min. After cooling, the reaction mixture was quenched with water (10 mL) and stirred for 15 min at room temperature. The mixture was poured in 50 mL of water and extracted once with Et_2O (50 mL) and

then with CH_2Cl_2 (50 mL). The combined organic layers were concentrated and the crude product was dissolved in Et_2O (50 mL) and extracted with 3 N HCl (50 mL). The acidic layer was made slighly alkaline with 50 % NaOH and the resulting layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The brown oil was treated with pentane to give **6.10a** as a white solid. The ^1H NMR spectrum of this material showed *i.a.* a singlet at δ = 3.70 ppm which was assigned to a small amount (< 5 %) of 1-methyl-4-phenylimidazole (**6.18b**, see text). This impurity was removed by crystallization from CH_2Cl_2/pentane to give **6.10a** as white crystals (0.32g, 75 %): mp. 131-132 °C (Lit.[31a] 128-129 °C); ^1H NMR (DMSO.d_6, 200 MHz): δ = 7.26-7.42 (m, 4H), 7.70-7.75 (m, 3H), 9.81 (br, 1H).

4(5)-(*p*-Nitrophenyl)imidazole (6.10b) and 1-ethyl 4-(*p*-nitrophenyl)imidazole :
p-Nitrophenyl-*N*-tosylaldimine (**6.5b**, 0.91 mg, 3.0 mmol) was allowed to react with TosMIC (0.64 g, 3.3 mmol) and K_2CO_3 (1.24 g, 9.0 mmol) in EtOH/DME 2:1 (30 mL) for 2 h, analogously to the procedure described for **6.10a** The mixture obtained upon acid/base extraction was chromatographed (Al_2O_3, CH_2Cl_2) to give two fractions. The second fraction gave **6.10b** as a orange solid (0.35 g, 62 %), pure according to ^1H-NMR. Yellow crystals were obtained by crystallization from EtOH (96 %): mp. 195-196 °C (Lit. [31a], 225 °C); ^1H NMR (DMSO.d_6, 300 MHz): δ = 7.71 (s, 1H), 7.81 (s, 1H), 7.90 (d, *J* = 8.8 Hz, 2H), 8.09 (d, *J* = 8.8 Hz, 2H), 12.20-12.60 (br, 1H); ^{13}C NMR (DMSO.d_6, 75.4 MHz): δ = 117.18 (s), 124.14 (d), 124.56 (s), 124.71 (d), 137.20 (d), 141.31 (s), 145.20 (d); MS (relative intensity, %): *m/z* = 28 (100), 32 (52.43), 63 (14.51), 89 (50.87), 116 (58.02), 131 (9.77), 143 (25.93), 159 (12.65), 189 (M^+, 100); HRMS: *m/z* calc. for $C_9H_7N_3O_2$: 189.054, found 189.054.
The first fraction gave a side product, *i.e.* the *N*-ethylated derivative of **6.10b**, as a yellow solid (160 mg, 25%), pure according to ^1H NMR. Yellow crystals were obtained by crystallization from CH_2Cl_2/hexane: mp 125-126 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.53 (t, *J* = 7.4 Hz, 3H), 4.06 (q, *J* = 7.4 Hz, 2H), 7.39 (d, *J* = 1.3 Hz, 1H), 7.57 (d, *J* = 1.3 Hz, 1H), 7.90 (d, *J* = 9.1 Hz, 2H), 8.23 (d, *J* = 9.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 16.16 (q), 42.13 (t), 116.68 (d), 124.01 (d), 124.66 (d), 137.52 (d), 139.90 (s), 140.55 (s), 145.98 (s); MS (relative intensity, %): *m/z* = 28 (75.6), 32 (16.3), 8.9 (11.0), 116 (17.6), 171 (27.2), 187 (10.5), 217 (M^+, 100); HRMS: *m/z* calc. for $C_{11}H_{11}N_3O_2$: 217.085, found 217.085.
When MeOH was used as cosolvent, 1-methyl-4-(*p*-nitrophenyl)imidazole (**6.18b**) was obtained as a yellow solid (0.08 g, 12 %). Yellow crystals were obtained by crystallization from CH_2Cl_2/hexane: mp 194-196 °C (Lit. [31b], 195 °C); ^1H NMR ($CDCl_3$, 500 MHz): δ = 3.76 (s, 3H), 7.34 (d, *J* = 1.3 Hz, 1H), 7.52 (d, *J* = 1.0 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 8.22 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 33.61 (q), 118.25 (d), 124.04 (d), 124.72 (d), 138.76 (d), 140.12 (s), 140.48 (s), 146.67 (s); MS (relative intensity, %): *m/z* = 28 (59.22), 32 (12.39), 89 (16.77), 116 (11.37), 142 (8.75), 157 (23.19), 173 (8.07), 203 (M^+, 100); HRMS: *m/z* calc. for $C_{10}H_9N_3O_2$: 203.068, found 203.068.

4(5)-(*p*-Tolyl)imidazole (6.10d) and 1-methyl-4-(*p*-tolyl)imidazole (6.18d) :
p-Tolyl-*N*-tosylaldimine (**6.5d**, 082 mg, 3.0 mmol) was allowed to react with TosMIC (0.64 g, 3.3 mmol), and K_2CO_3 (1.24 g, 9.0 mmol) in MeOH/DME 2:1 (33 mL) for 2 h, analogously to the procedure described for **6.10a**. The mixture obtained upon acid/base extraction was chromatographed (Al_2O_3, CH_2Cl_2) to give two fractions. The second fraction gave **6.10d** as a pale orange solid (0.25 g, 53 %), pure according to ^1H-NMR: mp 112-114 °C (Lit.[31b], 116-117

°C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.35 (s, 3H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.33 (br s, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.68 (br s, 1H), 11.73-11.80 (br, 1H); ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 21.04 (q), 115.76 (d), 124.78 (d), 129.32 (d), 129.82 (s), 135.51 (d), 136.55 (s), 137.94 (s); MS (relative intensity, %): *m/z* = 28 (80.94), 32 (18.14), 77 (6.60), 91 (10.70), 103 (9.37), 118 (7.29), 130 (16.62), 157 (23.73), 158 (M^+, 100); HRMS: *m/z* calc. for $C_{10}H_{10}N_2$: 158.084, found 158.084.

The first fraction gave a side product **6.18d**, *i.e.* the *N*-methylated derivative of **6.10d**, as a white solid (25 mg, 5 %), pure according to ^{1}H NMR. White crystals were obtained by crystallization from petroleum ether (bp 40-60 °C): mp 115-118 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.35 (s, 3H), 3.71 (s, 3H), 7.12 (d, *J* = 1.4 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.44 (d, *J* = 1.3 Hz, 1H), 7.65 (d, *J* = 8.1, 2H); ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 21.12 (q), 33.39 (q), 115.32 (d), 124.53 (d), 129.13 (d), 131.31 (s), 136.21 (s), 137.74 (d), 142.41 (s); MS (relative intensity, %): *m/z* = 77 (4.2), 103 (6.3), 130 (13.9), 172 (M^+, 100); HRMS: *m/z* calc. for $C_{11}H_{12}N_2$: 172.100, found 172.100.

1,3-Di[(4(5)-imidazolyl)benzene dihydrobromide (6.10f) :

N,N' -Ditosylisophthaldialdimine (**6.5f**, 0.88 g, 2.0 mmol) was allowed to react with TosMIC (**6.2**, 0.43 g, 2.2 mmol) and K_2CO_3 (1.21 g, 8.8 mmol) for 2 h, analogously to the procedure described for **6.10a**. The mixture obtained upon acid/base extraction contained **6.10f** and several methylated imidazoles. Attempts to isolate **6.10f** were not successful.

(*E*)-4(5)-(2-Phenylethenyl)imidazole (6.10h) and (*E*)-1-methyl-4-(2-phenylethenyl)imidazole (6.18h) :

N-Tosylcinnamaldimine (**6.5h**, 0.86 g, 3.0 mmol) was allowed to react with TosMIC (0. 64 g, 3.3 mmol) and K_2CO_3 (0.91 g, 6.6 mmol) for 2 h, analogously to the procedure described for **6.10a**. The mixture obtained upon acid/base extraction was chromatographed (Al_2O_3, CH_2Cl_2) to give two fractions. The second fraction gave **6.10h** as a white solid (0.25 g, 49 %) pure according to ^{1}H NMR: mp 174-178 °C (Lit.[36], 181.5 °C); ^{1}H NMR (DMSO.d_6, 300 MHz): δ = 6.90-7.58 (m, 9H), 11.90-12.30 (br, 1H); ^{13}C NMR (DMSO.d_6, 125.7 MHz): δ = 119.80 (br s), 124.96 (d), 125.81 (d), 126.77 (d), 126.85 (d), 128.68 (d), 136.31 (d), 137.45 (d); MS (relative intensity, %): *m/z* = 28 (47.00), 39 (18.31), 51 (15.52), 63 (19.12), 77 (9.93), 89 (14.02), 102 (5.43), 115 (82.33), 142 (39.71), 143 (26.74), 169 (100), 170 (M^+, 83.83); HRMS: *m/z* calc. for $C_{11}H_{10}N_2$: 170.084, found 170.084.

The first fraction gave a side product **6.18h**, *i.e.* the *N*-methylated derivative of **6.10h**, as a pale orange solid (50 mg, 10 %), pure according to ^{1}H NMR. White crystals were obtained by crystallization from CH_2Cl_2/hexane: mp 125-127 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.68 (s, 3H), 6.91 (d, *J* = 1.5 Hz, 1H), 6.98 (d, *J* = 16.1 Hz, 1H), 7.19-7.37 (m, 4H), 7.42 (br s, 1H), 7.48 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 33.29 (q), 118.19 (d), 120.06 (d), 126.07 (d), 126.73 (d), 126.88 (d), 128.42 (d), 137.58 (s), 138.06 (d), 140.08 (s); MS (relative intensity, %): *m/z* = 28 (100), 32 (22.30), 42 (22.93), 115 (19.88), 143 (26.53), 183 (98.13), 184 (M^+, 53.03); HRMS: *m/z* calc. for $C_{12}H_{12}N_2$: 184.100, found 184.100.

In a separate experiment, (*E*)-4(5)-(2-phenylethenyl)imidazole (**6.10h**, 0.10 g, 0.59 mmol), methyl *p*-toluenesulfonate (0.22 g, 1.18 mmol), and K_2CO_3 (0.15 g, 1.10 mmol) were refluxed for 135 min. After cooling, addition of H_2O (50 mL), extraction with Et_2O (2 x 50 mL), drying ($MgSO_4$), and removal of the solvent, the crude product was purified by column chromatography (Al_2O_3, CH_2Cl_2), to give, after washing the crude product with pentane, **6.18h** as a white

solid (0.75 g, 69 %): mp 176-179 °C, which was identical with the above material according to ^{1}H NMR. 2D-NMR (NOESY) was consistent with the 1,4-disubstituted imidazole structure of **6.18h**.

4(5)-(*p*-Chlorophenyl)imidazole (6.10k) and 4-(*p*-chlorophenyl)-1-methylimidazole (6.18k) :

p-Chlorophenyl-*N*-tosylaldimine (**6.5k**, 0.88 g, 3.0 mmol) was allowed to react with TosMIC (0. 64 g, 3.3 mmol), and K_2CO_3 (0.91 g, 6.6 mmol) for 2 h, analogously to the procedure described for **6.10a**. The mixture obtained upon acid/base extraction was chromatographed (Al_2O_3, CH_2Cl_2) to give two fractions. The second fraction gave **6.10k** as a white solid (0.30 g, 55 %), pure according to ^{1}H NMR: mp 140-143 °C (Lit.[37], 147 °C); 1H NMR (DMSO.d_6, 200 MHz): δ = 7.38 (d, *J* = 8.3 Hz, 2H), 7.65 (br s, 1H), 7.73 (d, *J* = 7.6 Hz, 2H), 7.80 (br s, 1H); ^{13}C NMR (DMSO.d_6, 125 MHz): δ = 113.05 (d), 125.85 (d), 128.40 (d), 130.22 (s), 133.85 (s), 136.08 (d), 138.85 (s); MS (relative intensity, %): *m/z* = 28 (70.58), 32 (16.52), 41 (23.42), 63 (17.04), 89 (47.35), 116 (19.28), 123 (16.03), 151 (16.48), 178 (M^+, 100); HRMS: *m/z* calc. for $C_9H_7ClN_2$: 178.030, found 178.030.

The first fraction gave a side product **6.18k**, *i.e.* the *N*-methylated derivative of **6.10k**, as a white solid (80 mg, 14 %), pure according to ^{1}H NMR. White crystals were obtained by crystallization from CH_2Cl_2/hexane: mp 144-145 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.71 (s, 3H), 7.14 (d, *J* = 1.4 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 0.9 Hz, 1H), 7.67 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 33.35 (q), 116.00 (d), 125.87 (d), 128.62 (d), 132.12 (s), 132.68 (s), 138.06 (d), 141.26 (s); MS (relative intensity, %): *m/z* = 28 (96.68), 32 (22.08) 150 (19.39) 192 (M^+, 100); HRMS: *m/z* calc. for $C_{10}H_9ClN_2$: 192.045, found 192.045; Anal. calc. for $C_{10}H_9ClN_2$: C, 62.35; N, 14.54; H, 4.71; Cl, 18.40, found C, 62.01; N, 14.42; H, 4.65; Cl, 18.39.

4(5)-(3,4-Dimethoxyphenyl)imidazole (6.10l) :

3,4-Dimethoxyphenyl-*N*-tosylaldimine (**6.5l**, 0.91 g, 3.0 mmol) was reacted with TosMIC (**6.2**, 0. 64 g, 3.3 mmol) and K_2CO_3 (0.91 g, 6.6 mmol) for 2 h, analogously to the procedure described for **6.10a**. The mixture obtained upon acid/base extraction was purified by washing with CH_2Cl_2 to give a pink solid (**6.10l**, 0.32g, 51 %), pure according to ^{1}H NMR: mp 166-168 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.74 (s, 3H), 3.79 (s, 3H), 6.92 (d, *J* = 8.1 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.35 (s, 1H), 7.47 (br s, 1H), 7.67 (br s, 1H), 12.05-12.30 (br, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 55.64 (q), 55.72 (q), 108.63 (d), 112.32 (d), 114.69 (s), 116.75 (d), 127.31 (s), 135.84 (d), 147.72 (s), 149.18 (s); MS (relative intensity, %): *m/z* = 28 (59.14), 32 (11.24), 63 (15.41), 76 (6.97), 77 (6.16), 91 (12.97), 118 (14.81), 161 (38.32), 189 (30.92), 204 (M^+, 100); HRMS: *m/z* calc.for $C_{11}H_{12}N_2O_2$: 204.090, found 204.090. Some *N*-methylated derivative was observed in ^{1}H NMR, but this side product was not isolated.

4(5)-(2-Furyl)imidazole (6.10m) and 4-(2-fuyl)-1-methylimidazole (6.18m) :

2-Furfuryl-*N*-tosylaldimine (**6.5m**, 1.50 g, 6.0 mmol) was reacted with TosMIC (1.29 g, 6.6 mmol), and K_2CO_3 (1.82 g, 13.2 mmol) for 2 h, analogously to the procedure described for **6.10a**. The mixture obtained upon acid/base extraction was chromatographed (Al_2O_3, CH_2Cl_2) to give two fractions. The second fraction gave a brown oil, which contained a mixture of **6.10m**, **6.18m**, and **6.19m** (5:1:2.3, 370 mg). The brown oil was dissolved in Et_2O (25 mL) and stirred vigoursly with NaOH (50 % in water, 25 mL) for 3 h. After separation, the basic

layer was acidified with H_2SO_4. The resulting acidic water layer was neutralized with saturated $NaHCO_3$ and extracted with Et_2O (2 x 25 mL). The organic layer was dried ($MgSO_4$), concentrated, and the brown oil obtained was crystallized from CH_2Cl_2/hexane to give pale **6.10m** as brown crystals (50 mg, 6 %), pure according to ^1H NMR: mp 115-116 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ = 6.43 (dd, *J* = 1.9 Hz, *J* = 1.8 Hz, 1H), 6.56 (d, *J* = 3.4 Hz, 1H), 7.31 (br s, 1H), 7.39 (d, *J* = 1.1 Hz, 1H), 7.69 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 104.25 (d), 111.19 (d), 114.31 (d), 131.65 (s), 135.29 (d), 140.92 (d), 148.78 (s); MS (relative intensity, %): *m/z* = 51 (11.4), 52 (12.8), 79 (25.6), 105 (19.1), 134 (100); HRMS: *m/z* calc. for $C_7H_6N_2O$: 134.048, found 134.049.

The first fraction gave, after crystallization from CH_2Cl_2/hexane, a side product **6.18m** as a pale yellow solid (50 mg, 6 %), pure according to ^1H NMR: mp 101-103 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ = 3.66 (s, 3H), 6.41-6.42 (m, 1H), 6.58 (dd, *J* = 0.9 Hz, *J* = 0.9 Hz, 1H), 7.07 (d, *J* = 1.4 Hz, 1H), 7.34 (dd, *J* = 0.8 Hz, *J* = 0.8 Hz), 7.38 (d, *J* = 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 33.30 (q), 103.76 (d), 111.03 (d), 115.59 (d), 134.81 (s), 137.81 (d), 140.59 (d), 149.93 (s); MS (relative intensity, %): *m/z* = 57 (10.3), 69 (18.1), 81 (11.9), 105 (14.3), 119 (19.7), 148 (M^+, 100); HRMS: *m/z* calc. for $C_8H_8N_2O$:148.064, found 148.066.

5-(*p*-Chlorophenyl)-1-tosylimidazole (6.12k) :

A mixture of TosMIC (0.64 g, 3.3 mmol), p-chlorophenyl-*N*-tosylaldimine (**6.5 k**, 0.88 g, 3.0 mmol), and K_2CO_3 (0.91, 6.6 mmol) in *t*-BuOH/DME 2:1 (33 mL) was refluxed for 20 h. After cooling, addition of H_2O (50 mL), extraction with Et_2O (2 x 50 mL), drying ($MgSO_4$), and removal of the solvent, the crude product was filtered through a short column of Al_2O_3 (CH_2Cl_2), to give, after washing with pentane, **6.12k** as white crystals (0.10 g, 10 %): mp 174-176 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.44 (s, 3H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 1.4 Hz, 1H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.87 (d, *J* = 8.4 Hz, 2H), 8.04 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 21.66 (q), 112.08 (d), 126.46 (d), 127.30 (d), 128.78 (d), 130.40 (d), 130.55 (s), 133.69 (s), 134.64 (s) 136.68 (d), 143.07 (s), 146.38 (s); MS (relative intensity, %): m/z = 28 (72.3), 63 (10.4), 91 (100), 92 (13.2), 123 (36.7), 125 (12.3), 150 (11.0), 155 (84.2), 177 (42.8), 332 (M^+, 73.2); HRMS calc $C_{16}H_{13}N_2O_2SCl$: 332.039, found 332.039.

5-(*p*-Chlorophenyl)-1,4-ditosyl-4*H*,5*H*-imidazoline (6.13k, R^1 = *p*-ClC_6H_4) :

A mixture of TosMIC (0.64 g, 3.3 mmol), *p*-chlorophenyl-*N*-tosylaldimine (**6.10m**, 0.88 g, 3.0 mmol), and K_2CO_3 (0.91, 6.6 mmol) in *t*-BuOH/DME 2:1 (33 mL) was refluxed for 2 h. After cooling, addition of water (50 mL), extraction with Et_2O (2 x 50 mL), drying ($MgSO_4$), and removal of the solvent, the crude product was filtered through a short column of Al_2O_3 (CH_2Cl_2), to give **6.13k** as a white solid (1.20 g, 82 %), pure according to ^1H NMR: mp 145-148 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.43 (s, 6H), 4.96 (d, *J* = 5.6 Hz, 1H), 5.29 (d, *J* = 5.4 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 2H), 7.24-7.35 (m, 5H), 7.57 (d, *J* = 7.8 Hz, 2H), 7.71-7.74 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 21.65 (q), 60.05 (d), 95.70 (d), 127.45 (d), 127.76 (d), 129.16 (d), 129.39 (d), 129.73 (d), 129.99 (d), 132.70 (s), 133.56 (s), 134.75 (s), 136.10 (s), 145.46 (s), 145.70 (s); MS (relative intensity, %): m/z = 28 (36.45), 65 (14.58), 91 (100), 155 (64.27), 333 (M^+-Tos, 72.83).

X-Ray crystal structure of 4-(*p*-Chlorophenyl)-1-methylimidazole (6.18k)

Crystal data : Formula: $C_{10}H_9N_2Cl$; M = 192.65, crystal color and habit: transparent colorless parallepiped, crystal size: 0.20 x 0.25 x 0.50 mm; orthorhombic; space group: $P2_12_12_1$; a =

5.464(1) Å, b = 8.429 (1) Å, c = 19.788 (2) Å; V = 911.4 (2) Å^3; Z = 4, ρ = 1.404 g/cm^3; μ = 3.7 cm^{-1}; F(000) = 400. *Data collection :* The data were collected on an Enraf-Nonius CAD-4F diffractometer (Mo tube, 50 kV, 40 mA, monochromated Mo-Kα radiation (λ = 0.71073 Å), Δω = 1.10 + 0.34 tg θ), interfaced to a MS-DOS computer; T = 130 K; θ range 1.04-27.5°; reflections collected: 4565; independent reflections: 2065. *Solution and refinement* [38]: The structure was solved by Patterson methods (DIRDIF) and refined anisotropically by full-matrix least squares based on $F_o^2>0$ (SHELXL-93); data/parameters 2013/154; data-to-parameter ratio: 13.1:1; R_1 = 0.0291 [$F_o>4.0\ \sigma(F_o)$], wR_2 = 0.0867 [I>0]; absolute-stucture parameter: Flack's **x**: -0.01(5); maximal residual electron density: 0.26(5) e/Å^3. The program PLUTO has been used for graphical representation of the crystal structure.

Table 6.4 : *Bond Lengths and Selected Bond Angles for Compound* ***6.18k*** *(Excluding H Atoms)*

Interatomic Distances (Å)					
Cl(1)-C(1)	1.7407(17)	N(2)-C(10)	1.459(2)	C(4)-C(5)	1.397(2)
N(1)-C(7)	1.380(2)	C(1)-C(2)	1.387(2)	C(4)-C(7)	1.463(2)
N(1)-C(8)	1.319(2)	C(1)-C(6)	1.383(2)	C(5)-C(6)	1.380(2)
N(2)-C(8)	1.344(2)	C(2)-C(3)	1.388(2)	C(7)-C(9)	1.369(2)
N(2)-C(9)	1.362(2)	C(3)-C(4)	1.397(2)		

Bond Angles (deg.)					
C(7)-N(1)-C(8)	105.14(14)	C(1)-C(2)-C(3)	118.98(15)	C(4)-C(7)-C(9)	128.54(14)
C(8)-N(2)-C(9)	107.39(14)	C(2)-C(3)-C(4)	120.80(15)	N(1)-C(7)-C(9)	109.48(14)
C(8)-N(2)-C(10)	125.96(15)	C(3)-C(4)-C(5)	118.37(15)	N(2)-C(9)-C(7)	106.08(14)
C(9)-N(2)-C(10)	126.59(15)	C(3)-C(4)-C(7)	120.90(14)	N(1)-C(7)-C(4)	121.89(14)
Cl(1)-C(1)-C(2)	119.32(12)	C(5)-C(4)-C(7)	120.70(14)	N(1)-C(8)-N(2)	111.91(14)
Cl(1)-C(1)-C(6)	119.10(15)	C(4)-C(5)-C(6)	121.55(15)	C(2)-C(1)-C(6)	121.58(15)
C(1)-C(6)-C(5)	118.70(15)				

6.6 References and Notes

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